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Raising HDL-cholesterol and lowering CHD risk: does intervention work?

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Epidemiological studies have associated low HDL-cholesterol with an increased risk of morbid coronary events. Accordingly, intervention to correct low HDL-cholesterol may be cardioprotective. A number of randomized intervention studies have addressed this hypothesis using fibrates (the Veterans Affairs HDL Intervention trial, the Helsinki Heart Study, and the Bezafibrate Infarction Prevention trial), or nicotinic acid, alone [Coronary Drug Project (CDP)] or in combination [the HDL Atherosclerosis Treatment Study (HATS) and the Stockholm Ischaemic Heart Disease study (IHD)]. These trials demonstrate conclusively that treatments to increase HDL-cholesterol deliver clinically significant improvements in prognosis. Of these trials, the largest improvement in outcomes occurred in the HATS trial, where the incidence of a combined coronary endpoint (coronary death, non-fatal myocardial infarction, confirmed stroke, or revascularization for worsening ischaemia) was reduced by 60–90% in patients receiving treatment based on nicotinic acid combined with a statin. The benefits of nicotinic acid-based treatment appear to be durable, as significant outcome benefits were visible in the group of patients initially randomized to nicotinic acid in the CDP 15 years after randomization, i.e. 9 years after the end of double-blind treatment. The combination of nicotinic acid with a statin appears to be a rational, effective, and safe strategy for minimizing cardiovascular risk in patients with dyslipidaemia.

Introduction

An abundance of epidemiological evidence identifies low HDL-cholesterol as an independent risk factor for coronary heart disease.[1–4] For example, the Framingham study found that HDL-cholesterol was the principal factor accounting for coronary risk in men and women and was significantly associated in men and women with all coronary heart disease ($P < 0.001$), 'coronary attacks' ($P < 0.01$), and angina pectoris ($P < 0.01$–0.001), and this association persisted after adjustment for other lipid parameters.[1] This US experience was confirmed in a large European cohort, in the Prospective Cardiovascular Münster (PROCAM) study, which also demonstrated a significant relationship between low HDL-cholesterol and elevated cardiovascular risk after correction for other factors.[5] An analysis of data from the Framingham study, the Coronary Primary Prevention Trial, and Multiple Risk Factor Intervention Trial indicates that each decrease in HDL-cholesterol of 1 mg/dL (0.03 mmol/L) was associated with an increase in the risk of coronary heart disease of 2% in men and 3% in women.[6]

Recent research has defined the pleiotropic cardioprotective actions of HDL-cholesterol and the multiple pathogenetic links between low HDL-cholesterol and atherosclerotic disease.[7,8] However, epidemiological and mechanistic data alone are insufficient to guide therapy aimed at reducing the burden of cardiovascular disease. Only well-designed and carefully executed clinical trials in relevant patient populations can provide the

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evidence base for therapeutic interventions. The purpose of this review is to consider the evidence showing that intervening specifically to increase HDL-cholesterol results in clinically meaningful improvements in cardiovascular outcomes in patients with dyslipidaemia. There are potentially many ways to increase HDL-cholesterol and three of these will be considered in detail: lifestyle-based interventions (diet and exercise), synthetic approaches to increasing HDL-cholesterol (gene therapy or administration of a synthetic form of HDL-cholesterol), and pharmacologic interventions.

Lifestyle interventions

Lifestyle interventions are, rightly, regarded as the cornerstone of intervention to reduce cardiovascular risk. More than two decades ago, the Framingham Offspring study defined an inverse relationship between the level of obesity and the HDL-cholesterol, which was present irrespective of age or gender.[9] In addition, the main Framingham study showed that increasing obesity is a key factor driving the trend towards lower HDL-cholesterol with advancing age.[10] Other lifestyle factors are also implicated. Data from the US National Heart, Lung, and Blood Institute show that smoking more than 20 cigarettes per day was associated with a marked decrease in HDL-cholesterol levels, whereas taking exercise for at least 1 h each day and moderate alcohol consumption increased serum HDL-cholesterol.[11] These data confirm the negative effects of smoking and the positive effects of exercise and moderate alcohol consumption on circulating levels of HDL-cholesterol, reported from other evaluations in the US and European populations.[12–15]

Cross-sectional evidence suggests that the deleterious changes in HDL-cholesterol associated with lifestyle factors are reversible with appropriate lifestyle-based interventions. For example, evidence from the Framingham Offspring study shows that HDL-cholesterol levels were not lower in ex-smokers, who had not smoked for a year or more, compared with participants who had never smoked.[14] Data from intervention studies are less clear, although improvements in HDL-cholesterol have been observed in patients receiving interventions based on diet and/or exercise in some, but not in all studies.[16–19] A pooled analysis of two trials evaluating the effects of a diet and exercise regimen demonstrated an increase in HDL-cholesterol of 0.1 mmol/L and a decrease in triglycerides of 0.2 mmol/L after 1 year of treatment.[20]

Overall, it appears that lifestyle interventions may result in moderate improvements in cardiovascular risk factors, at least for some patients, and reductions in levels of obesity that may result from such interventions are highly desirable. However, as far as HDL-cholesterol is concerned, the magnitude of the benefit is likely to be modest, and it remains uncertain to what extent HDL-cholesterol can be increased and where this parameter was low at baseline.[21] Moreover, we await prospectively acquired evidence of positive effects on clinical outcomes through lifestyle interventions. Other interventions to produce clinically significant increases in HDL-cholesterol are likely to be required for many patients.

Synthetic interventions

Experimental findings

Experimental studies, involving the production of transgenic animals that over-express human apolipoprotein (apo) AI (the principal apo species in present HDL-cholesterol particles), have helped to elucidate the role of HDL-cholesterol in cardioprotection. Cholesterol-fed rabbits transgenic for human apoAI developed identical elevations of LDL-cholesterol and VLDL-cholesterol, compared to control animals, whereas levels of HDL-cholesterol in the transgenic animals were about twice as high as those in the control animals throughout the study.[22] After 14 weeks of cholesterol feeding, the proportion of the surface of the thoracic aorta covered by atherosclerotic lesions in the transgenic group was half when compared with that of the control group (15 vs. 30%, $P < 0.01$). Similarly, the cholesterol content of the aorta of transgenic animals was about half that of the control animals (116 vs. 247 μmol/g, $P < 0.01$). Although aortic atherosclerosis is not a common feature of atherogenesis in humans, the authors of this study point out that important aspects of cholesterol metabolism and the morphological features of the atherosclerotic plaques are highly reminiscent of the process of atherosclerosis in humans.

A further study involved over-expression of the apoA-I/C-III/A-IV gene cluster in mice, resulting in simultaneous elevation of HDL-cholesterol, hypercholesterolaemia, and a gross hypertriglyceridaemia (8–10-fold elevation relative to control).[23] Despite this complex dyslipidaemic profile, the deposition of atherosclerotic material in the aortic sinus was 61% lower in the transgenic animals than in the controls ($P < 0.001$). These experimental data support the epidemiological findings in humans relating to the independent nature of low HDL-cholesterol as a risk factor for atherosclerotic disease as discussed earlier.

Cardioprotective properties of apoA-IMilano

ApoA exists in two major forms: apoA-I and apo-II. HDL-cholesterol containing apoA-I is believed to offer greater cardioprotection than HDL-cholesterol containing apoA-II or both apoA-I and apoA-II.[24] ApoA-IMilano (apoA-I_M) is a genetic variant of apoA-I, first identified more than two decades ago in three members of a family living in Limone sul Garda, a remote, and until recently isolated, village in Northern Italy.[25–27] ApoA-I_M contains an amino acid substitution (arginine 173 to cysteine) that permits the formation of disulfide bridges, leading to the formation of homodimers and heterodimers with apoA-II. It is believed that the mutation stems from a single mating couple in the 18th century. A survey conducted in 1985 revealed 33 living carriers of the mutation, among a population of about 1000

individuals. The mutation is transmitted as an autosomal dominant trait, and all known current carriers are heterozygous for the mutation. Carriers of apoA-I_M present with extremely low levels of HDL-cholesterol but were apparently without signs of cardiovascular disease.

A survey of cardiovascular risk factors was conducted in 21 carriers of apoA-I_M and 42 control subjects matched for age and gender.[28] Two further groups of control subjects with hypoalphalipoproteinaemia (HA), also matched for age and gender, were identified using records from a lipid clinic and a blood donor clinic, respectively ($n = 21$ for each). These subjects had HDL-cholesterol below the 10th percentile for Italian subjects with no history of cardiovascular disease. There were no significant differences between the apoA-I_M and the control group in age, gender, body mass index, systolic and diastolic blood pressures, or plasma glucose. However, mean HDL-cholesterol in apoA-I_M carriers [0.5 mmol/L (20 mg/dL)] was less than half that in controls [1.3 mmol/L (48.7 mg/dL)] and was lower than that observed in either HA group [0.75 mmol/L (29 mg/dL) and 0.70 mmol/L (27 mg/dL)]. Otherwise, apart from a modest hypertriglyceridaemia, the lipid profile was unremarkable. The intima-media thickness (IMT) of the carotid artery provided an index of early vascular disease. Both HA groups demonstrated marked and significant ($P < 0.05$) increase in the average carotid IMT measured at three sites (0.86 and 0.88 mm) when compared with the control group (0.64 mm). In contrast, IMT in the apoA-I_M group (0.63 mm) did not differ significantly from the control.

A randomized, double-blind, placebo-controlled multicentre study evaluated the effects of recombinant apoA-I_M on atheroma burden in patients with acute coronary syndromes and an angiographic finding of a $\geq$20% obstruction of the lumen of a coronary artery within 14 days of an acute coronary syndrome event (unstable angina or myocardial infarction).[29] A total of 57 patients were randomized to placebo or one of two doses of a recombinant apoA-I_M–phospholipid complex (rapoA-I_M, 15 or 45 mg/kg, given as five weekly infusions) in a 1:2:2 ratio. Data are available from 47 patients who completed the study. Target segments of coronary arteries were identified for intravascular ultrasound on the basis of $\leq$50% luminal narrowing over a length of $\geq$30 mm in a major epicardial vessel. The total atheroma volume and the average maximum thickness of atheroma in the target coronary segment were markedly and significantly reduced by the rapoA-I_M treatment (*Figure 1*). Similar effects were noted on the maximum thickness of atheroma in the target coronary segment.

These studies showed that carriers of this genetic variant of apoA-I were at low risk of cardiovascular disease, despite an apparently atherogenic lipid profile. Moreover, treatment of patients with acute coronary syndromes with recombinant apoA-I_M for only 5 weeks induced a marked reversal of atherosclerosis. This was a pilot study of limited size, and a lower severity of atheroma in placebo group, on average, and the lack of an apparent dose-related effect of apoA-I_M suggest the need for some caution in interpreting the results of the intervention study. Nevertheless, these studies indicate the possible future potential of interventions based on increasing the cardioprotective properties of HDL-cholesterol.

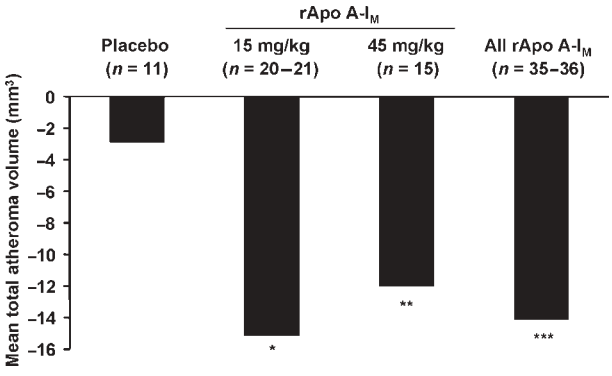

Figure 1 Reversal of atherosclerosis in patients with acute coronary syndromes treated with recombinant apoA-I_M for 5 weeks: data from a randomized, placebo-controlled study. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. baseline. Drawn from data presented by Nissen *et al*.[29]

Pharmacologic interventions

Fibrates

The Veterans Affairs HDL Intervention Trial

The Veterans Affairs HDL Intervention Trial (VA-HIT) was a randomized, double-blind, placebo-controlled, parallel-group multi-centre trial designed to test the hypothesis that raising HDL-cholesterol with a fibrate would improve outcomes in men with low HDL-cholesterol who were at high risk of a cardiovascular event.[30] Eligible participants were men aged <74, with HDL-cholesterol $\leq$1.0 mmol/L ($\leq$40 mg/dL), LDL-cholesterol $\leq$3.6 mmol/L ($\leq$140 mg/dL), triglycerides $\leq$3.4 mmol/L ($\leq$300 mg/dL), and a history of coronary heart disease, defined as a history of myocardial infarction, angina with evidence of myocardial ischaemia, coronary revascularization, or angiographic evidence of >50% stenosis of at least one major epicardial coronary artery. The primary endpoint was the combined incidence of non-fatal myocardial infarction and death from coronary heart disease.

A total of 2531 patients were randomized to gemfibrozil 1200 mg/day or placebo for a mean follow-up of 5.1 years.[31] Patients had a lipid profile consistent with isolated low HDL-cholesterol at baseline [mean HDL-cholesterol 0.8 mmol/L (32 mg/dL), mean LDL-cholesterol 2.9 mmol/L (112 mg/dL), and mean triglycerides 1.8 mmol/L (161 mg/dL)]. The intention to recruit a population at high risk of coronary events was successful, as 61% of randomized patients had a history of MI, 57% of patients were hypertensive, and 25% of patients had a diagnosis of diabetes at baseline.

Lipid parameters were measured after 12–18 months of treatment.[31,32] When compared with the placebo arm,

HDL-cholesterol in the gemfibrozil arm was 6% higher, total cholesterol was 4% lower, and triglycerides were 31% lower. Slightly larger improvements occurred in normoglycaemic subjects vs. subjects with diagnosed diabetes with regard to HDL-cholesterol (+8 vs. +5%, respectively, $P = 0.02$) and triglycerides (−29 and −20%, respectively, $P < 0.001$).[33] LDL-cholesterol was unchanged by gemfibrozil in all patients or after stratification for diagnosis of diabetes.

Gemfibrozil treatment significantly reduced the risk of the primary endpoint of the trial: the combination of death from coronary heart disease and non-fatal myocardial infarction (*Figure 2*). The individual endpoints of non-fatal myocardial infarction, hospitalization for congestive heart failure, and stroke were also significantly reduced, whereas reductions of similar magnitude in the risk of death from coronary heart disease or revascularization marginally failed to achieve statistical significance (*Figure 2*). Marked reductions were also observed in the risk of transient ischaemic attacks (by −59% for gemfibrozil vs. placebo, $P < 0.001$) and the risk of undergoing carotid endarterectomy (−65%, $P < 0.001$).

Subgroup analyses showed that raising HDL-cholesterol with gemfibrozil significantly improved cardiovascular outcomes irrespective of age, diagnosis of diabetes, or levels of HDL-cholesterol, LDL-cholesterol, or triglycerides. A larger benefit was observed in patients with myocardial infarction (risk reduction −27%, $P = 0.002$) when compared with patients without such a history (risk reduction −19%, $P =$ NS), which is not surprising as a prior myocardial infarction confers a higher cardiovascular risk and potentially greater benefits from intervention.

A multi-variate analysis of the effects of lipid parameters on outcomes indicated that a change in HDL-cholesterol of the magnitude observed during the study, but not the corresponding observed changes in LDL-cholesterol or triglycerides, could account for a significant improvement in the primary endpoint of the study.[32] We can be confident, therefore, that the outcome benefits observed in the VA-HIT study resulted primarily from increases in HDL-cholesterol.

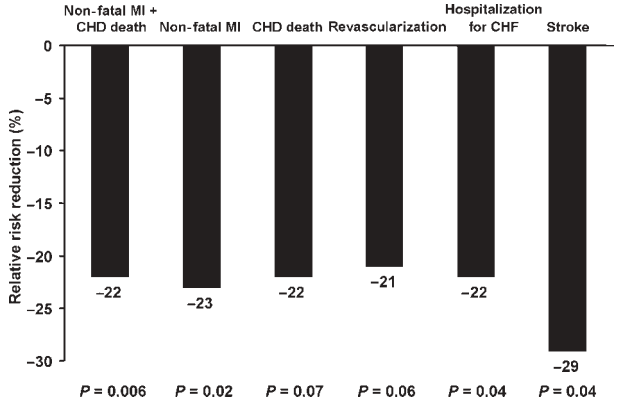

Figure 2 Selected clinical outcomes from the VA-HIT. Columns show relative risk reductions for gemfibrozil vs. placebo. CHD, coronary heart disease; CHF, congestive heart failure. Drawn from data presented by Rubins *et al.*[31]

Helsinki Heart Study

The Helsinki Heart Study (HHS) was a randomized, double-blind, 5 year evaluation of the effects of gemfibrozil on clinical outcomes.[34] The patient population consisted of a total of 4081 men aged 40–55, with non-HDL cholesterol ≥5.2 mmol/L (≥200 mg/dL). Patients were randomized to receive gemfibrozil 1200 mg/day ($n = 2051$) or placebo ($n = 2030$). Treatment with gemfibrozil improved HDL-cholesterol by 11% from baseline over the study period, whereas decreases were observed in non-HDL-cholesterol (−14%), LDL-cholesterol (−11%), and triglycerides (−35%).[34,35] The incidence of coronary heart disease events (all myocardial infarction or cardiac death) was reduced by 34% (95% CI 8–53, $P = 0.02$) in the gemfibrozil group, relative to placebo, although no significant change in total mortality occurred.

After multi-variate adjustment for cardiovascular risk factors (age, blood pressure, smoking, alcohol use, baseline lipid levels, physical activity, and body weight) using the Cox proportional hazards model, treatment-induced changes in HDL-cholesterol and LDL-cholesterol remained significantly associated with the reduction in the incidence of coronary heart disease.[35] Changes in triglycerides, in contrast, had relatively little effect. The results of the HHS support those of the VA-HIT study in that increases in HDL-cholesterol were important drivers of improved cardiovascular outcomes in each case.

Bezafibrate Infarction Prevention Program

The Bezafibrate Infarction Prevention Program (BIP)[36] recruited a high-risk patient population ($n = 3090$) with established coronary disease (previous myocardial infarction or stable angina), HDL-cholesterol ≤1.2 mmol/L (≤45 mg/dL), triglycerides ≤3.4 mmol/L (≤300 mg/dL), LDL-cholesterol ≤4.7 mmol/L (≤180 mg/dL), and total cholesterol between 4.7 mmol/L (180 mg/dL) and 6.5 mmol/L (250 mg/dL). Patients were randomly assigned to receive bezafibrate 400 mg/day or placebo for a mean follow-up of 6.2 years. The primary endpoint was fatal or non-fatal myocardial infarction or sudden death.

Although bezafibrate increased HDL-cholesterol by 18% and reduced triglycerides by 21%, no significant change in the primary endpoint was observed (risk reduction (−9.4%, $P = 0.26$). However, subgroup analyses suggested a significant effect of the fibrate on outcomes in patients with a more adverse lipid profile. Specifically, significant reductions in the primary endpoint were observed in patients with triglycerides ≥2.3 mmol/L (>200 mg/dL) at baseline (risk reduction 39.5%, $P = 0.02$) and in patients with HDL-cholesterol ≤0.9 mmol/L (≤35 mg/dL), and triglycerides ≥2.3 mmol/L at baseline (risk reduction (−41.5%, $P = 0.02$)). However, no significant risk reduction was observed in patients with hypertriglyceridaemia and HDL-cholesterol >0.9 mmol/L.

Nicotinic acid

The Coronary Drug Project

This randomized, double-blind, placebo-controlled trial enrolled a high-risk population with at least one prior

myocardial infarction, although patients were excluded for a myocardial infarction within the previous 3 months or evidence of recent worsening of coronary heart disease.[37] Patients were initially randomized to one of six treatment groups, involving treatment with nicotinic acid 3000 mg/day ($n = 1119$), clofibrate 1800 mg/day ($n = 1103$), D-thyroxine 6 mg/day ($n = 1110$), oestrogens 2.5 mg/day ($n = 1101$), oestrogens 5 mg/day ($n = 1119$), or placebo ($n = 2789$). The primary endpoint was total mortality; secondary endpoints were the incidence of coronary events or stroke/transient ischaemic attacks. Patients were followed for an average of 6.2 years of double-blind treatment. Clofibrate did not significantly improve clinical outcomes, whereas the thyroxine and oestrogen arms were terminated early, due to tolerability concerns.

Treatment with nicotinic acid improved total serum cholesterol by 9.9% from baseline and decreased triglycerides by 26.1% from baseline. Data were not presented for HDL-cholesterol, but the effects on these other lipid parameters are typical of those seen in patients receiving nicotinic acid,[38] and it is reasonable to assume that HDL-cholesterol would have been elevated in this population. Cardiovascular outcomes (the primary endpoint of non-fatal myocardial infarction and cardiovascular death, non-fatal myocardial infarction, death from coronary heart disease, and need for cardiovascular surgery) improved significantly after double-blind treatment with nicotinic acid (*Figure 3A*).[37] Reductions in the risk of all-cause mortality or coronary mortality were not observed in the nicotinic acid group. However, a significant mortality benefit has been demonstrated in these patients in an analysis conducted 15 years after the initial randomization, i.e. 9 years after the study closed (*Figure 3B*).[39] Treatment with nicotinic acid in the Coronary Drug Project (CDP) was associated with a significant reduction in all-cause mortality and coronary death in the overall patient population. In addition, the mortality benefit was observed irrespective of whether patients had fasting plasma glucose at baseline above or below 5.6 mmol/L (100 mg/dL); the cut-off value for the diagnosis of impaired fasting glucose.[40] Subsequent analyses of the CDP database have confirmed that the prognostic benefits associated with nicotinic acid in the CDP were preserved irrespective of the presence of impaired fasting glucose, type 2 diabetes, or the metabolic syndrome.[41,42]

The HDL Atherosclerosis Treatment Study

The rationale, design, and results of the HDL Atherosclerosis Treatment Study (HATS)[43] are discussed in detail in the accompanying review by Professor G. Brown. However, for completeness, the principal results of this important study will be summarized here. HATS was a randomized, double-blind, placebo-controlled trial in a population with established coronary heart disease, $\geq$50% stenosis of one coronary vessel or $>$30% stenosis of three coronary vessels. The trial also set out to recruit a population with low HDL-cholesterol [$\leq$0.9 mmol/L ($\leq$35 mg/dL) in men or $\leq$1.0 mmol/L ($\leq$40 mg/dL) in women]. Patients were randomized to receive nicotinic acid 2000 mg/day + simvastatin 10–30 mg/day ($n = 33$), nicotinic acid + simvastatin ± antioxidant vitamins ($n = 33$), antioxidant vitamins ($n = 39$), or placebo ($n = 34$). The duration of double-blind treatment was 3 years.

Mean HDL-cholesterol at baseline was 0.8 mmol/L (31 mg/dL). Nicotinic acid + simvastatin markedly improved HDL-cholesterol (mean change from baseline of +29 vs. +6% with placebo, $P < 0.001$) and LDL-cholesterol (−43 vs. −9% with placebo). Regression of coronary atherosclerosis was observed with nicotinic acid + simvastatin

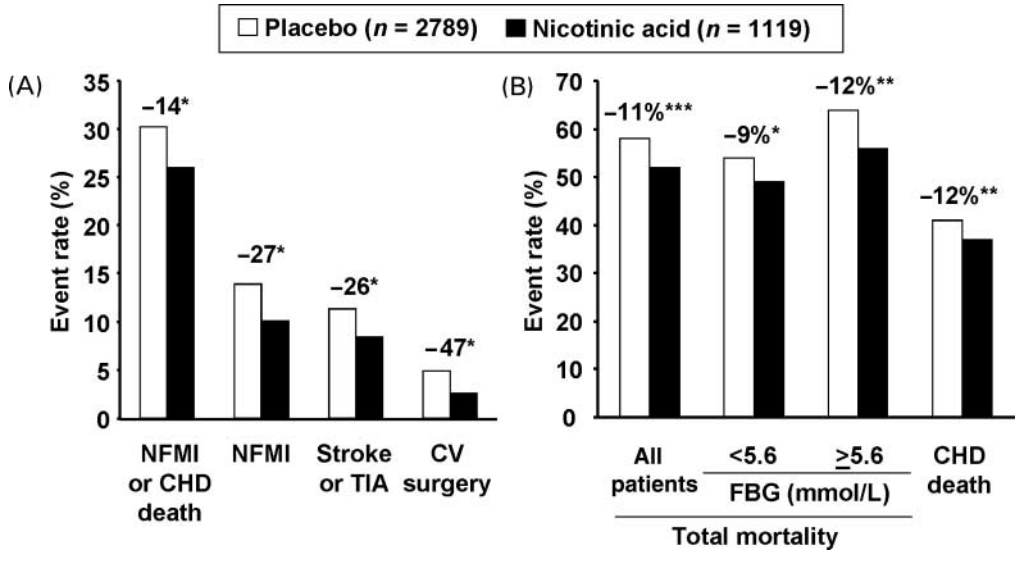

Figure 3 Clinical outcomes in the CDP. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. placebo. Data for the double-blind phase were for complete follow-up (average 6.2 years), except for cardiovascular surgery, which are 5 year data. NFMI, non-fatal myocardial infarction; CHD, coronary heart disease; TIA, transient ischaemic attack; CV, cardiovascular. Drawn from data presented by the CDP Research Group.[37,39] (A) Outcomes at the end of double-blind treatment. (B) 15 year outcomes (9 years following the end of double-blind treatment).

in 1273 lesions in nine proximal coronary artery segments, while atherosclerosis progressed on placebo. In addition, coronary patency improved with nicotinic acid + simvastatin vs. placebo irrespective of the degree of arterial stenosis at baseline, with the largest regression of atherosclerosis occurring in arterial segments with stenosis >50% at baseline.

The risk of a composite endpoint (coronary death, non-fatal MI, confirmed stroke, or revascularization for worsening ischaemia) was 90% lower in the nicotinic acid + simvastatin group vs. the placebo group at study end ($P = 0.03$). Considering all patients who received nicotinic acid + simvastatin or placebo (with or without antioxidant vitamins), the risk of this endpoint was still significantly lower in the groups receiving nicotinic acid (60% reduction vs. placebo ± antioxidants, $P = 0.02$).

The Stockholm Ischaemic Heart Disease Study

The Stockholm IHD Study randomized 555 patients with a previous myocardial infarction to combination treatment with open-label nicotinic acid (up to 3000 mg/day) and clofibrate (2000 mg/day) or to a control group receiving usual care for 5 years.[44] Total cholesterol decreased by 13% and triglycerides by 19% in the active treatment group (data on HDL-cholesterol were not provided). Total mortality and CHD mortality were reduced significantly in patients randomized to nicotinic acid + clofibrate [risk reductions of 26% ($P < 0.05$) and 36% ($P < 0.01$), respectively]. The benefit for total mortality was determined irrespective of age, as a risk reduction for this endpoint of 28% was observed in patients aged >60 at baseline.

Statins

Statins exert relatively little effect on levels of HDL-cholesterol, but are nevertheless effective in reducing the risk of coronary events in patients with low HDL-cholesterol. The Lipoprotein and Coronary Angiography Study (LCAS) compared fluvastatin with placebo in patients with low vs. higher HDL-cholesterol.[45] Angiographic data were available from 339 patients, of whom 68 (20%) had baseline HDL-cholesterol <0.9 mmol/L (<35 mg/dL). Mean HDL-cholesterol in the groups with lower and higher HDL-cholesterol were 0.8 mol/L (32 mg/dL) and 1.2 mmol/L (47 mg/dL), respectively. In the low HDL-cholesterol group, the mean change from baseline in the minimum lumen diameter of coronary atherosclerotic lesions was 0.065 mm for the statin vs. 0.274 mm for the placebo ($P < 0.0004$). In patients with higher HDL-cholesterol at baseline, mean changes in minimum lumen diameter were 0.036 mm with the statin and 0.083 mm with the placebo (P = NS). The difference in angiographic outcomes between the lower and higher HDL-cholesterol groups was statistically significant ($P = 0.01$).

The West of Scotland Coronary Prevention Trial (WOSCOPS) evaluated the effects of a different statin, pravastatin, on clinical outcomes in 6595 patients with hypercholesterolaemia.[46] The patient population of this trial contained individuals with a wide range of HDL-cholesterol levels, permitting stratification of the patient population for this parameter.[47] Patients with low HDL-cholesterol were at higher risk of an adverse cardiovascular outcome, as would be expected (*Figure 4*) These patients gained more in absolute terms from statin therapy but, in relative terms, the proportionate risk reduction produced by the statin was the same across the quartiles of HDL-cholesterol. Similar conclusions have been drawn from other evaluations of statins.[48] Whether effects on HDL-cholesterol levels influence these findings is unclear. However, it is clear that patient populations with low HDL-cholesterol derive greater benefit from intervention with a statin than patients with higher HDL-cholesterol.

Discussion

Epidemiological cohort studies have convincingly associated low HDL-cholesterol with increased cardiovascular risk and suggest strongly that interventions to increase HDL-cholesterol will yield clinically significant outcome benefits. The improvements in HDL-cholesterol arising from lifestyle interventions are worthwhile, especially given the likely additional health benefits, in terms of weight loss, amelioration of insulin resistance, and so on. Nevertheless, pharmacological interventions to raise HDL-cholesterol will be required by most patients to optimize effects on cardiovascular risk. The results of well-designed pharmacological interventions aimed at increasing HDL-cholesterol (fibrates or nicotinic acid) have confirmed the therapeutic potential of HDL-cholesterol raising. Among these, the long-term (15 year) benefits arising from treatment with nicotinic acid in the CDP stand out, as does the unprecedented 60–90% reduction in cardiovascular risk seen with a combination of nicotinic acid and a statin in HATS.

Given the finding that patients with low HDL-cholesterol benefit the most in absolute terms from statins, the combination of nicotinic acid and a statin appears to be a rational and effective strategy for minimizing cardiovascular risk in patients with low HDL-cholesterol. In addition, reports of an increased risk of rhabdomyolysis in patients receiving a statin combined with a fibrate

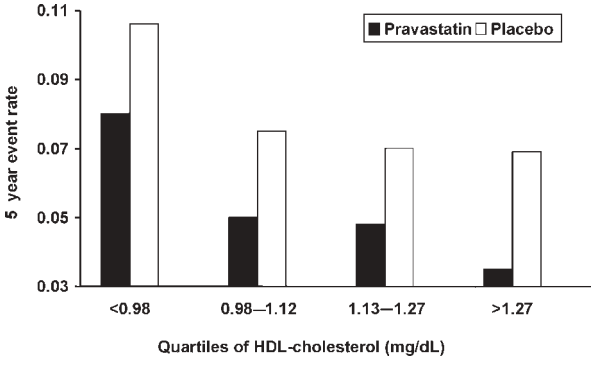

Figure 4 Cardiovascular event rates stratified for patients' HDL-cholesterol at baseline in the West of Scotland Coronary prevention study (WOSCOPS). Reproduced with permission from West of Scotland Coronary Prevention Study Group.[47]

(particularly gemfibrozil) may inhibit the use of such combinations in routine clinical practice.[49] No such safety concerns have been raised for nicotinic acid, though this agent is associated with a high incidence of flushing (mainly for immediate-release preparations) and has been associated with hepatic side-effects (mainly for slow-release preparations). A new prolonged-release formulation of this agent provides equivalent efficacy on the lipid profile to standard, immediate-release nicotinic acid with a significantly lower incidence of flushing and apparently minimal potential for hepatotoxicity.[50] This new formulation may simplify the delivery of HDL-cholesterol raising therapy in routine clinical practice.

Conclusions

Low HDL-cholesterol is strongly associated with increased cardiovascular risk, and interventions to correct low HDL-cholesterol significantly improve cardiovascular outcomes. Combination therapy with statins and nicotinic acid provides a rational and effective strategy for minimizing cardiovascular risk, which is well supported by clinical evidence.

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